PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY
(CHAPTER I OR CHAPTER II
OF THE PATENT COOPERATION TREATY)
(PCT Rules 44*bis*.3(c) and 72.2)

To:

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Received / Empfangen
Ritscher & Partner AG
Dat: 11. Sep. 2006
Ref:
Frist:

Date of mailing *(day/month/year)* 08 September 2006 (08.09.2006)	
Applicant's or agent's file reference 50005PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/CH2004/000610	International filing date *(day/month/year)* 01 October 2004 (01.10.2004)
Applicant ETH ZÜRICH et al	

1. **Transmittal of the translation to the applicant.**

☐ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).

☑ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

2. **Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

KR

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. **Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

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Form PCT/IB/338 (January 2004)

TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
50005PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CH2004/000610	01.10.2004	01.10.2003
International Patent Classification (IPC) or national classification and IPC		
C12N15/10		
Applicant		
ETH ZÜRICH		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____ , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CH2004/000610

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (Rule 12.3 and 23.1(b))
- ☐ publication of the international application (Rule 12.4)
- ☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☐ the international application as originally filed/furnished

☒ the description:

pages 1-38 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1-19 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/5-5/5 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CH2004/000610

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-19	NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

1. This report makes reference to the following documents:

D1: SEPP A ET AL: "Microbead display by in vitro compartmentalisation: selection for binding using flow cytometry" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, Vol. 532, No. 3, 18 December 2002 (2002-12-18), pages 455-458, XP004398450 ISSN: 0014-5793

D2: US-A-5 856 090 (EPSTEIN DAVID M) 5 January 1999 (1999-01-05)

D3: WO 98/37186 A (ANDREWS DAVID; ACTINOVA LTD (GB); ISAKSEN MORTEN (GB); LINDQVIST BJOR) 27 August 1998 (1998-08-27)

D4: WO 02/066653 A (XENCOR INC) 29 August 2002 (2002-08-29)

D5: DOI N ET AL: "STABLE: protein-DNA fusion system for screening of combinatorial protein libraries in vitro." FEBS LETTERS. 27 AUG 1999, Vol. 457, No. 2, 27 August 1999 (1999-08-27), pages 227-230, XP002312563 ISSN: 0014-5793

D6: GULL M ET AL: "Screening for receptor ligands

using large libraries of peptides linked to the c terminus of the lac repressor." PNAS. March 1992, Vol. 89, No. 5, March 1992 (1992-03-00), pages 1865-1869, XP002043736 ISSN 0027-8424

3. The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-19 does not involve an inventive step (PCT Article 33(3)).

3.1 **D5** describes a method for the *in vitro* linking of phenotype and genotype based on the linking of streptavidin-polypeptide conjugates with the biotinylated nucleic acids coding therefor in microcompartments.

Following further consideration, document **D5** is considered the prior art closest to the subject matter of independent claim 1 and discloses a **non-covalent** *in vitro* coupling of genotype and phenotype using polypeptide-peptide fusions. **D5** also indicates that although STA was used therein as fusion partner, other DNA-binding proteins can also be used as adapters (page 229, right-hand column, lines 3-5). More particularly, **D5** refers to document **D6**, which describes fusion proteins with a lac repressor as the constant DNA-binding part. The subject matter of claim 1 thus differs from the teaching of document **D5** in that the coupling between the genotype and the phenotype is **covalently** occasioned by the polypeptide-peptide

fusion protein.

The current invention can therefore be considered to address the problem of developing an alternative method for the *in vitro* evolution of polypeptides.

The solution to this problem as proposed in claim 1 of the present application cannot be considered inventive (PCT Article 33(3)) for the following reasons:

D3 describes a method for the ***in vitro*** production of peptide or protein expression libraries, which reflects a diverse population of peptides or proteins, the peptides and proteins covalently binding to the DNA coding therefor as fusion proteins by using the "nicking" property of the replication initiator of the *E.coli* bacteriophage P2A as fusion partner.

A person skilled in the art familiar with **D5** and seeking further DNA-binding proteins would, without thereby being inventive and whilst also being familiar with **D3** (the prior art already shows ***in vitro*** methods for producing peptide or protein expression libraries in which **covalent** coupling takes place between the genotype and the phenotype), combine the technical properties of the two prior art documents (D5 and D3) in order to arrive at the same result as in independent claim 1.

3.2 Dependent claims 2-19 do not contain any features which, in combination with the features of any claim to which they refer, meet the PCT requirements for novelty and inventive step; see document **D2**.

D2 describes an ***in vivo*** method for coupling genotype and phenotype, methylase-polypeptide fusions being covalently bonded to plasmid DNA which contain the sequence 5'-GGFC-3'.

D4 discloses an *in vivo* method for screening prokaryotic host cells containing DNA coding for a fusion protein, consisting of a nucleic acid for a nucleic acid-modified enzyme (NAM) and a nucleic acid for a candidate protein, operatively bonded to a promoter and an EAS (enzyme attachment sequence) sequence, which is recognised by the NAM enzyme and thus allows covalent coupling of the genotype and the phenotype.

Even though the methods depicted in **D2** and **D4** are ***in vivo*** methods, all the remaining technical features are identical to those as per dependent claims 2-19. It would have been obvious to a person skilled in the art familiar with document **D5** to transfer the technical features from **D2 or D4** to an *in vitro system* and to thus arrive at the same result as in dependent claims 2-19.